American Journal of Medical Genetics 69:287–289 (1997)

Brief Clinical Report

Frontonasal Malformation With Tetralogy of Fallot Associated With a Submicroscopic Deletion of 22q11

Robert F. Stratton[1]* and René M. Payne[2]
[1]*South Texas Genetics Center, San Antonio*
[2]*Central Texas Genetics Center, Austin*

We report on a 14-month-old girl with bifid nasal tip and tetralogy of Fallot. Several similar patients have been described with CNS or eye abnormalities. Chromosome analysis with FISH, using Oncor DiGeorge probes, confirmed a submicroscopic deletion of 22q11. Many patients with Shprintzen (velo-cardio-facial) syndrome have a similar deletion with conotruncal cardiac defects and an abnormal nasal shape, suggesting that a gene in this area, possibly affecting neural crest cells, influences facial and other midline development. Am. J. Med. Genet. 69:287–289, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: deletion, 22q11; tetralogy of Fallot; nose; bifid; frontonasal dysplasia

INTRODUCTION

The primary signs of frontonasal dysplasia (FND) are ocular hypertelorism, broad nasal root, bifid nasal tip and widow's peak [Temple et al., 1990]. DeMoor et al. [1987] reported 3 children with bifid nasal tip, hypertelorism and tetralogy of Fallot (TOF). Two more patients with FND and TOF had a lipoma of the anterior corpus callosum [Meguid, 1993] and ocular colobomata [Temple et al., 1990]. One additional patient with FND had valvar aortic stenosis [Meineke and Blunck, 1989]. We report on a 14-month-old girl with bifid nasal tip and TOF. FISH with Oncor DiGeorge probes showed a submicroscopic deletion of 22q11.

Clinical Report

The patient was born at term to a healthy 20-year-old primagravida woman after an uncomplicated pregnancy. Maternal family history was unremarkable, and no information about the father was provided. Birth weight was 2.3 kg (<3rd centile) and length was 43 cm (–3 SD). A bifid nose was noted at birth and a cardiology evaluation showed tetralogy of Fallot. There was initial hypocalcemia and poor feeding, with a total nursery stay of 8 days. The patient was hospitalized for viral pneumonia at 2 months. She had repair of the TOF with revision for bleeding at age 14 months. Two days later she suffered a stroke with a subsequent seizure. Renal sonogram was normal. She had chronic constipation and GE reflux demonstrated by barium swallow. She began sitting at 6 months, but regressed developmentally after her stroke. She recently began saying "mama" non-specifically.

Physical examination at age 14 months showed a length of 71.3 cm (<5th centile), weight of 7.3 kg (–3.2 SD) and OFC of 44.9 cm (10th centile). She was brachycephalic (cephalic index 0.88) with symmetric occipital flattening. The coronal sutures were not ridged and there was no widow's peak. Inner canthal distance was 26 mm, interpupillary distance 45 mm (both 50th centile) and outer canthal distance was 68 mm (15th centile). The anterior segment of the eyes appeared normal. The nasal bridge was flattened and the tip was full and depressed with a midline groove and very short columella (Fig. 1). The philtrum was 7 mm and relatively flat. The vermilion border of the upper lip was thin and tented. There was a prominent maxillary frenulum with diastema of the central incisors. The right ear measured 39, the left 40 mm and both were normally placed and shaped. The chest was normal except for post-surgical scars and a pacemaker. The umbilicus appeared highly implanted and had redundant skin. Total hand length was 83 mm (5th centile) with single palmar creases. The thumbs appeared long and low-placed. Fingertip dermatoglyphics showed WUUUU on the left and WUUWU on the right. The axial triradii were slightly distal and ulnar placed. The nails were normal as were the rest of the physical findings.

Chromosome analysis showed a 46,XX normal female karyotype. FISH with Oncor DiGeorge probes

*Correspondence to: Dr. Robert Stratton, South Texas Genetics Center, 730 North Main, Suite 615, San Antonio, TX 78205.

Received 5 February 1996; Accepted 22 July 1996

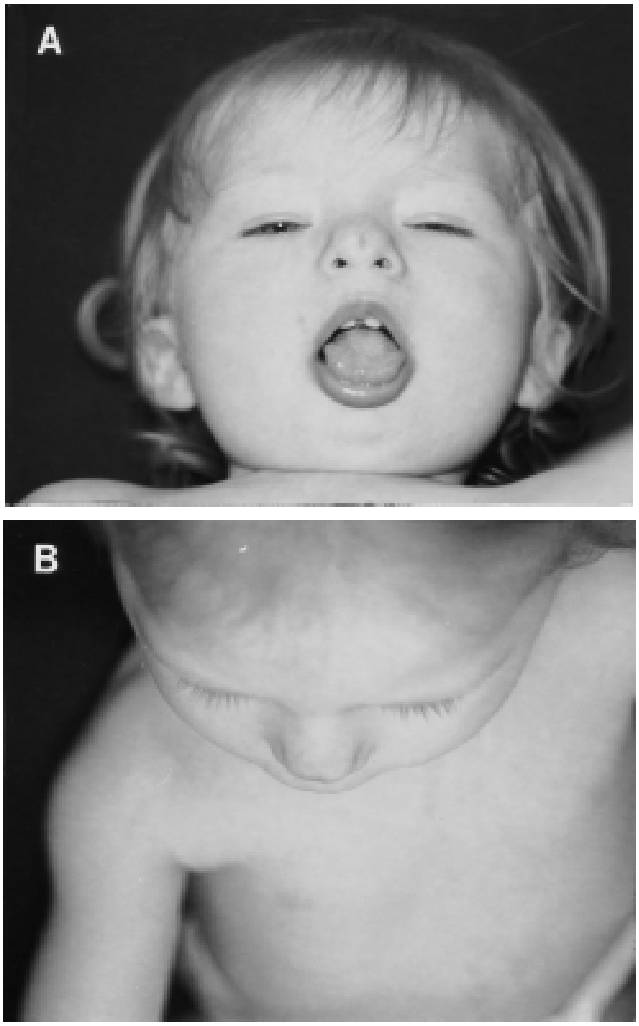

Fig. 1. **A, B:** Patient at 14 months of age, showing bifid nasal tip and maxillary diastema.

(D22S75) showed signal on only one chromosome 22, confirming a submicroscopic deletion in the DiGeorge region at 22q11.

DISCUSSION

According to Sedano and Gorlin [1988] FND consists of true ocular hypertelorism, broad nasal root, median facial cleft, unilateral or bilateral clefting of the alae nasi, lack of formation of the nasal tip, anterior cranium bifidum occultum, and V-shaped extension of hair onto the forehead (widow's peak). The history and pertinent signs of the condition are reviewed by Gorlin et al. [1990].

DeMoor et al. [1987] first described 3 children with height, weight and OFC proportionately below the 3rd centile. All had hypertelorism, grooved nasal tip and tetralogy of Fallot. Chen et al. [1987, 1992] reported a 36 week gestation female with frontonasal malformation, iris colobomata, TOF and multiple other brain and systemic abnormalities associated with duplication of 2q from a balanced maternal t(2;7)(q31;q36) translocation. Meinecke and Blunck [1989] reported on a 26-month-old mildly retarded boy with short stature, microcephaly, relative hypertelorism, broad flat nasal bridge and tip and valvar aortic stenosis. They considered this patient strikingly similar to the patients of DeMoor et al. [1987]. Patient 3 of Temple et al. [1990] had hypertelorism, a broad nasal root and tip with a central raised strand of tissue on the nose, and TOF. She also had bilateral colobomata. Her OFC was at the 10th centile and she was developmentally delayed. Chromosomes were normal. Mequid [1993] reported on a 6-year-old boy with obvious FND, lipoma of the anterior corpus callosum, TOF and ASD. His height was in the 25th centile and weight and OFC were in the 3rd centile. His IQ was 80. High resolution chromosomes were normal, Fryns et al. [1993] reported on a 20-year-old woman with a frontonasal malformation and apparently balanced 15q22;22q13 translocation inherited from her mother, who was not mentioned to be abnormal. Stevens and Qumsiyeh [1995] reported on a 4-year-old boy with frontonasal dysostosis, ASD, absent corpus callosum, abnormal left hemisphere gyral pattern and ventricle on CT scan and other midline abnormalities. He had an apparently balanced complex translocation 46,XY,t(7;3)(3;11)(q21.3;q27;q23;q21).

Our patient has a nasal malformation with bifid tip and short columella, relative but not true hypertelorism, and apparent midline widening of the maxilla with a large diastema of the central incisors. She does not have cranium bifidum or widow's peak and does not fulfill Sedano and Gorlin's [1988] criteria for FND. Her brachycephaly could suggest craniofrontonasal dysplasia but she is not as severely affected as one would expect for this entity. Her bifid nose may be an isolated trait, unrelated to the heart defect and chromosome abnormality. Several cases of isolated and familial bifid nasal tip are discussed by Sedano and Gorlin [1988]. Alternatively, her nasal configuration may be causally related to the submicroscopic 22q11 deletion.

In her review of neurocristopathies, Jones [1990] lists several malformations, sequences and syndromes in which altered cranial neural crest development is implicated. These include anterior chamber defects of the eye, cardiac aorticopulmonary septation defects, frontonasal dysplasia and DiGeorge anomaly.

Deletion of 22q11.2 is found in a wide range of syndromes including DiGeorge anomaly, conotruncal anomaly face syndrome [Matsuoka et al., 1994] and many patients with Shprintzen (velo-cardio-facial) syndrome [Lindsay et al., 1995]. This latter syndrome includes a wide nasal root and tip. Our patient's findings suggest that a gene(s) within the DiGeorge critical area is (are) responsible for development of the nose. The patient of Fryns et al. [1993] had a mild form of frontonasal dysplasia and an apparently balanced 15q22; 22q13 translocation inherited from her normal mother. It is possible that their patient had a submicroscopic loss of 22q material at the breakpoint, or coincidentally had a separate 22q deletion.

Altered development of cranial neural crest cells may be involved in frontonasal malformations and FND, but it is likely that more than one gene influences cell migration. The patient of Stevens and Qumsiyeh [1995] had a complex chromosome rearrangement, not

involving chromosome 22. They suggest that the breakpoints may help locate the gene(s) involved in FND and other midline craniofacial malformations. Unfortunately, they did not do FISH with DiGeorge probes to ascertain if the complex rearrangement was a coincidental finding. The patient of Chen et al. [1987] had segmental aneuploidy that was a more likely cause of the physical findings, although FISH with DiGeorge probes was not available at that time.

While it is uncertain that FND is caused by a deletion of 22q, a subset of patients with frontonasal malformation associated with other neural crest related defects, such as aorticopulmonary septation defects, midline CNS anomalies and anterior segment defects of the eye may be. FND with TOF may not be a separate syndrome, as suggested by De Moor et al. [1987] and Meguid [1993]. It is probably appropriate to do FISH with DiGeorge probes on this subset of patients, although FISH may not detect a small intragenic deletion or point mutation until the genes are cloned.

REFERENCES

Chen H, Rightmire D, Fowler M, Zapata C, Hogan G, Wolfson J (1988): Frontonasal malformation and dup (2q) syndrome. Am J Med Genet [Suppl 4]:191–192.

Chen H, Rightmire D, Zapata C, Fowler M, Hogan G, Wolfson J, Meunke M (1992): Frontonasal dysplasia and arhinencephaly resulting from unbalanced segregation of maternal t(2;7)(q31;q36). Dysmorphology Clin Genet 6:99–106.

De Moor MA, Baruch R, Human DG (1987): Frontonasal dysplasia associated with tetralogy of Fallot. J Med Genet 24:107–109.

Fryns JP, Kleczkowska A, van der Berghe H (1993): Frontonasal malformation and reciprocal translocation t(15;22)(q22;q13). Clin Genet 44: 46–47.

Gorlin RJ, Cohen MM, Levin S (1990): "Syndromes of the Head and Neck." New York: Oxford Press, pp 785–788.

Jones MC (1990): The neurocristopathies: Reinterpretation based upon the mechanism of abnormal morphogenesis. Cleft Palate J 27:136–140.

Lindsay EA, Goldberg R, Jurecic V, Morrow B, Carlson C, Kucherlapati RS, Shprintzen RJ, Baldini A (1995): Velo-cardio-facial syndrome: Frequency and extent of 22q11 deletions. Am J Med Genet 57:514–522.

Matsuoka R, Takoa A, Kimura M, Imamura S-I, Kondo C, Joh-o K, Ikeda K, Nishibatake M, Ando M, Momma K (1994): Confirmation that the conotruncal anomaly face syndrome is associated with a deletion within 22q11.2. Am J Med Genet 53:285–289.

Meguid NA (1993): Frontonasal dysplasia, lipoma of the corpus callosum and tetralogy of Fallot. Clin Genet 44:95–97.

Meinecke P, Blunck W (1989): Frontonasal dysplasia, congenital heart defect, and short stature: a further observation. J Med Genet 26:408–409.

Sedano HO, Gorlin RJ (1988): Frontonasal malformation as a field defect and in syndromic associations. (Oral Surg Oral Med Oral Pathol 65: 704–710.

Stevens CA, Qumsiyeh MB (1995): Syndromal frontonasal dysostosis in a child with a complex translocation involving chromosomes 3,7,11. Am J Med Genet 55-494–497.

Temple IK, Brunner H, Jones B, Burn J, Baraitser M (1990): Midline facial defects with ocular colobomata. Am J Med Genet 37:23–27.